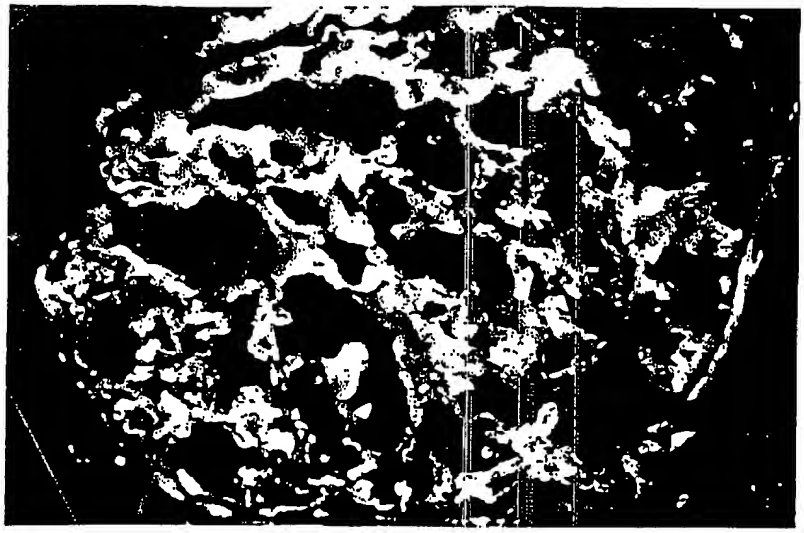

FIG. 11. Type III (immune-complex) injury in an SLE renal biopsy specimen. This patient had proteinuria and red blood cells in her urine. Note the granular (sometim s called "lumpy-bumpy") distribution of the immune deposits in this section stained with antibody to human C3.

early spontaneous abortion and may be an important cause of thrombotic disease in the general population.

Tissue damage may also be mediated through antibodies to neutrophil cytoplasmic antigens (ANCAs). These IgG antibodies, initially detected by immunofluorescence, have been divided by staining patterns into perinuclear (p-ANCA) and cytoplasmic (c-ANCA). p-ANCAs are directed against myeloperoxidase, while c-ANCAs are specific for proteinase 3 (221). These autoantibodies are useful markers for vasculitis, including Wegener's granulomatosis, pauciimmune necrotizing and crescentic pauciimmune glomerulonephritis, and polyarteritis nodosa, and their titers correlate with disease severity. The mechanism by which antibodies to these cytoplasmic antigens leads to blood vessel damage and inflammation is incompletely understood, but it may involve expression on activated neutrophils of proteinase 3 and myeloperoxidase, and possibly release of free proteinase 3. Antibodies to these molecules may provoke enhanced neutrophil chemotaxis and adhesion, together with triggering of the respiratory burst. This may lead to a series of events culminating in activation of T cells and macrophages and the formation of necrotizing granulomas.

APPROACHES TO THE TREATMENT OF SYSTEMIC AUTOIMMUNE DISEASE

In general, the management of human systemic autoimmune disease is empirical and unsatisfactory. For the most part, broadly immunosuppressive drugs, such as corticosteroids, are used in a wide variety of severe autoimmune and inflammatory disorders; in milder conditions, antiinflammatory agents acting on eicosenoid metabolism are often sufficient.

In addition to corticosteriods, other immunosuppressive agents are used in management of the systemic autoimmune diseases. Cyclophosphamide is an alkylating agent that causes profound depletion of both T- and B-lymphocytes and impairment of cell-mediated immunity. It is used in SLE nephritis and is particularly effective in granulomatous vasculitis and polyarteritis nodosa. Its use entails the risks of immunosuppression, along with an increased incidence of lymphoreticular malignancies. Azathioprine and the closely related 6-mercaptopurine are used in parallel situations; these are somewhat less effective but are less toxic.

Cyclosporine, tacrolimus, and mycophenolate mofetil are natural products with specific properties of T-lymphocyte suppression, and they have been used with success in SLE, RA, and, to a limited extent, in vasculitis and myositis. They have significant renal toxicity in addition to their immunosuppressive effects.

Methotrexate is widely used as a "second-line" agent in RA, with the goal of reducing disease progression. It is also useful in polymyositis and other connective-tissue diseases. Its mechanism of action here is controversial and may relate to its action on adenosine receptors rather than to its more familiar role as an antimetabolite.

There is optimism that more specific treatment for autoimmune disorders can be devised when their mechanisms become better understood. Oral tolerance holds promise as a means of attracting immunosuppressive T-lymphocytes to sites of active autoimmune pathology and suppressing inflammation by a bystander effect, probably involving TGF-β (271). Other approaches under development are monoclonal antibodies that are intended to block the acti n of cytokines or to deplete lymphocytes (204). With the exception of anti–TNF-α in RA (205), these have been disappointing.

CONCLUSIONS

The mechanisms of systemic autoimmune disease are diverse and incompletely understood. Several points are worthy of emphasis. The rules and restrictions governing ordinary immune responses seem to apply to autoimmune responses: there is little that is extraordinary about the immunoglobulin or TCR genes used or in their means of rearrangement or diversification; antigen is required to initiate responses. Production of and response to cytokines and other mediators is similar to what is seen for responses to exogenous antigens, and T and B cells collaborate in an MHC-restricted fashion. The availability of transgenic and knock-out mice and continuing progress in the understanding of the genome seem likely to open novel and fruitful approaches to understanding disorders of systemic autoimmunity.